

Center for Regulatory Effectiveness®

Suite 700

11 Dupont Circle, NW

Washington, DC 20036

Tel: (202) 265-2383 Fax: (202) 939-6969

www.TheCRE.com

June 18, 2004

Via e-mail and mail

Dr. Barbara Shane
NTP Executive Secretary
National Institute of Environmental Health Sciences
P.O. Box 12233
MD A3-01
Research Triangle Park, NC 27709

Dear Dr. Shane and Members of the NTP Board of Scientific Counselors:

Re: Written comments on the 12th RoC nominations and the
RoC review process, for the June 29, 2004 meeting of the
NTP Board of Scientific Counselors

I am submitting these comments as written comments and do not plan to deliver oral comments at the June 29 meeting, although I might be able to attend. The requested contact information is included as an attachment.

We have serious concerns regarding the two talc nominations. We believe that if an RoC review goes forward using those nominations, the resulting background document and any RoC listing would not comply with the Data Quality Act and its guidelines, which require that information disseminated to the public be clear and accurate. The Data Quality issues presented by the talc nominations and potential listing may also be pertinent to future nominations for other exposures.

We are also concerned with the failure of the NTP to promulgate its new RoC review procedures prior to proceeding with the 12th RoC.

At the conclusion of these comments, we make specific recommendations for Board action to address these matters, and we urge that our recommendations be discussed openly at the June 29 meeting.

Inadequacy of the talc nominations

The talc nominations are inadequate, and pose serious Data Quality problems, because they do not contain a clear, scientifically accurate definition of “talc” which would permit an accurate scientific review for potential RoC listing. Consequently, any listing, and any background document, based on such nominations would be inaccurate, unclear, and misleading, and therefore would not comply with the Data Quality Act and the OMB, HHS, and NIH guidelines.¹

Nominations to list “asbestiform talc” and non-asbestiform talc” were considered for the 10th RoC. CRE commented on that review, and we have re-reviewed the transcript of the RoC Subcommittee meeting of December 14, 2000 during which the Subcommittee debated those nominations. In the Draft Background Document for the 10th RoC nominations, talc was characterized as similar to asbestos, and was assumed to contain asbestos. At the RoC Subcommittee meeting, however, commenting mineralogists informed the Subcommittee that the term “asbestiform talc” was a misnomer because talc hardly ever occurs in an asbestiform habit, and anything that might be regarded as “asbestiform talc” was at best a mineralogic curiosity which has no practical significance. During the RoC Subcommittee meeting, the “asbestiform talc” nomination was therefore clarified by the NTP to mean talc containing asbestiform fibers, and not containing asbestos – in other words, pure talc intermixed with other minerals, not including asbestos, which had an asbestiform habit. The RoC Subcommittee then discussed literature on exposures to talc apparently containing asbestiform fibers. That literature pertained almost exclusively to certain deposits in the State of New York, which contain a mineral mixture which has been referred to in the literature as “New York talc” or “Gouverneur talc” to distinguish it from talc with its accepted scientific definition. The Subcommittee cast an evenly split vote on a recommendation to list talc containing asbestiform fibers which are not asbestos as a “reasonably anticipated human carcinogen”.

The 10th RoC review of the “non-asbestiform talc” nomination, which is another way of saying simply “talc”, was complicated by the fact that the literature indicated that some brands of such talc used for cosmetic purposes were contaminated with asbestos when testing of their content was conducted prior to 1976. In 1976, in order to address this situation, the Cosmetic, Toiletries, and Fragrance Association promulgated a cosmetic talc purity standard requiring that all cosmetic talc be completely free of asbestos. Because all of the epidemiologic studies involving cosmetic talc involved exposures substantially prior to 1976, it appeared that the slight reported increases in risk reported in the studies (almost none of which were statistically significant) could well have been the result of asbestos contamination as an historical exposure

¹ These guidelines can be accessed through the CRE website (www.TheCre.com) under “Data Quality” (left hand menu) and then “Data Quality Guidelines” (top menu). The RoCs are identified in the NIH guidelines as an informational document subject to the guidelines. (Sections III,6 and V, 2, d.)

that was no longer relevant to current exposures. This was one reason expressed by RoC Subcommittee members for discounting such studies. RoC Subcommittee members also clearly expressed concerns about the weakness of the risk results in the studies, the lack of a dose-response pattern, the potential for recall bias, and lack of a plausible mechanism of carcinogenic action, all of which also detracted from a “credible” causal interpretation as required by the listing criteria. The Subcommittee voted decisively, 8 to 2, against listing non-asbestiform talc as a “reasonably anticipated human carcinogen” in the 10th RoC.²

Subsequently, NTP decided to not proceed with a final decision on the talc nominations for the 10th RoC and announced that it would defer review pending further careful review of the literature “to determine if a clear definition of the agent or agents involved in human exposures can be developed.” This written statement was made by the NTP Director to stakeholders, and was disseminated on the NTP RoC website³, in the Introduction to the 10th RoC, and to the Board of Scientific Counselors⁴.

The new nominations for “Talc” -- “cosmetic talc”, and “occupational exposure to talc”-- do not provide the promised, and necessary, clear definition of the exposures. The nominations are both for exposure to “talc”. Talc has a “clear definition” in the scientific community. Talc has a CAS Registry number, 14807-96-6, and is defined as a hydrous magnesium silicate with a specific chemical formula and structure. Importantly, it does not include asbestos or any other minerals. In other words, “talc” is the pure mineral “talc”. To define and review talc as other than that would be scientifically inaccurate, confusing, and misleading.⁵ But the new talc nominations do not contain a “clear definition” of the nominated exposures because they do not include the CAS Registry number which contains a clear scientific definition of “talc”.

² There were seven votes in favor of a motion not to list, two against the motion, and one vote to defer (and not list in the 10th RoC) unless significant new data and analysis were brought forward. When the two members who voted for listing were questioned by the Chair regarding their reasoning, one did not supply any rationale, and the other supplied a rationale which was in conflict with the literature data set out in the Draft Background Document.

³ <http://ntp-server.niehs.nih.gov/NewHomeRoc/Talcstatus.html>.

⁴ Minutes of the BSC meeting on September 17-18, 2002.

⁵ A revised nomination for talc intermingled with asbestos would also be misleading and superfluous, since asbestos is already listed in the RoCs as a “known human carcinogen”, and therefore a mixture containing asbestos would also be considered a “known human carcinogen”. Asbestos also has its own CAS Registry number (as do a number of other minerals that might be intermingled with talc in occupational exposures).

The failure to include a CAS Registry number for a nominated exposure is at odds with established RoC precedent. Whenever a CAS number has been available for a nominated specific substance, it has been used. See Appendix H of the 10th RoC.

The “Basis” given for the talc nominations (in the Federal Register notice and the posted background materials for the June 29 Board meeting) state that the review of talc was deferred because of “confusion in the scientific literature over the mineral nature of talc”. That statement appears to be substantially inaccurate. There has been virtually no confusion in the scientific literature, or within the scientific community, over the mineral nature of “talc”. Talc is consistently defined in the literature, as well as by regulatory agencies, consistent with its CAS description, and has been distinguished from other minerals such as asbestos. Whatever confusion exists in the literature concerns mainly whether the studied exposures were to “talc” or to “talc” contaminated or mixed with asbestos (as in the epidemiologic studies involving exposure to pre-1976 cosmetic talc), or with asbestiform fibers that resembled asbestos (as in the worker studies involving so-called “New York talc”).

Historically, the NTP has avoided review of occupational exposures for the RoCs in cases where it appeared that the exposures differed geographically or over time, as expressly noted in Appendix A of the 10th RoC. Occupational exposures of talc miners, millers, and processors are of this type. As Dr. Huff, one of the NIEHS presenters for the talc review, stated near the beginning of his presentation: “Virtually every talc deposit is unique in chemistry and morphology.” (Tr. at 50.)

In a somewhat different vein, we note also that the “occupational exposure” nomination for “talc” is stated to apply not only to mining, but also to milling and processing. Like the exposures from mining, exposures from milling and processing vary widely from the definition of “talc”, since they often involve talc mixed with other minerals, which are likely to be present in greater quantities than the talc. Exposures from milling and processing are also likely to differ substantially from mining exposures. This also was noted during the RoC Subcommittee deliberations for the 10th RoC.

Furthermore, we have recently searched the literature for new studies on either exposure to cosmetic talc or occupational exposures to talc and other minerals and found only studies that further serve to emphasize the differences between relatively pure “talc” and talc that is intermingled with asbestos or asbestos-like fibers (in New York State). It appears that there are no significant new data to support nominations for “talc” – *i.e.*, talc without asbestos or asbestiform fibers – and therefore the new nominations and review would be a second review of the same substance without new support after a decisive RoC Subcommittee vote against listing. We believe this is a bad precedent for RoC reviews since it is likely to be perceived as lacking in

objectivity.⁶ The RoC Subcommittee deliberations on the talc nominations for the 10th RoC were extended and very thorough.⁷ It seems appropriate to ask why the talc review was deferred, then renewed with essentially the same data, rather than concluded with a decision not to list based on the RoC Subcommittee's overwhelming vote in favor of not listing talc not containing asbestiform fibers (which is what the scientific community means by "talc").

In summary, the new talc nominations do not provide a clear definition of "talc" because they do not incorporate the accepted scientific definition of talc as reflected in its CAS Registry number and description; and the nominations therefore seem to imply that the talc nominated for listing is something else which is not defined. This should be considered scientifically inaccurate, unclear, and likely to be misleading. Moving ahead with the RoC review process on the basis of such nominations will almost surely lead to a background document, and possibly a listing, which would violate the Data Quality standards for accuracy, clarity, and utility.

The need to finalize revisions to the RoC review process

At the January 2004 public meeting on the RoC review process, NTP staff announced that a revised review process would be used for the 12th RoC.⁸ The 12th RoC nominations have been announced without any NTP statement putting in place new procedures. Following publication of the nominations, CRE was informally advised by NTP that revised review procedures would be used, and that the revisions would include a commitment to make available to the public for comment the background documents before the RG1 and RG2 reviews, but the revised procedures have not been promulgated as of the date of these comments. The release of background documents for public comment prior to RG1 review would be an important and much needed revision. In the past, background documents have often not been released for comment until after the RG1 and RG2 reviews (or, more recently, sometimes after the RG1 review). We urge the NTP to publish revised procedures which codify this important change as

⁶ The RoC review procedures require that nominations contain a rationale for listing supported by "appropriate background information and relevant data". See Section V of the 10th RoC.

⁷ There is a public transcript of the proceedings. The talc portion is at pages 47 to 357 on Dec. 14, 2000.

⁸ The NTP also convened a special external expert panel to receive the public comments on the review process and the listing criteria. That panel was charged with providing recommendations to the NTP. We note that the background materials for the RoC portion of the Board's June 29, 2004 meeting do not include any mention of a report and recommendations from the panel.

soon as possible, and we urge the Board of Scientific Counselors to support this specific change in the review procedures.⁹

Recommendations for Board and NTP action

We recognize that the Board functions as an advisory body, not a decisionmaking body, which discusses issues and makes recommendations to the NTP Director. However, it also appears that it oversees the RoC review process and the decisions of its RoC Subcommittee to some extent.¹⁰ We therefore urge the Board to make the following recommendations to the NTP Director:

Regarding the new talc nominations –

1. The Director should reconsider his approval of the nominations because they do not provide the “clear definition” of exposures which he promised would have to be developed before any new review was approved.¹¹
1. Any nomination(s) for a re-review of talc should not be approved unless talc is “clearly defined” by reference to its CAS Registry number and description.
1. New talc nominations should not be approved even with reference to the talc CAS Registry number and description unless the Director (or another NTP authority charged with approval of nominations) is satisfied that there are significant new data supporting a new review which have become available since the decisive RoC

⁹ CRE also urged the NTP and the external review panel for RoC procedures to revise the nomination procedures to provide an opportunity for public comment on proposed nominations before they were sent to the Director for approval. This has also been suggested in the past by Board of Scientific Counselors members. It appears from the Federal Register notice of the 12th RoC nominations that this recommendation was rejected. If it had not, the problems discussed herein with the talc nominations might have been avoided.

¹⁰ A Board FACA report indicates that the Board approved or concurred in the listing recommendations of the RoC Subcommittee for the 10th RoC; however, the report does not indicate that the Board approved the decision to defer the talc review, nor does a report indicate that the Board has previously considered a rationale for renewing the talc review with nominations containing revised wording.

¹¹ Oddly, the Federal Register notice announcing the nominations and signed by the Director states that the current review procedures (those in effect on May 19, 2004) will apply, and those procedures provide for RG1 review and approval of nominations for sufficiency rather than approval by the Director.

Subcommittee vote against listing of non-asbestiform talc (which is consistent with the CAS definition).

1. If a revised nomination(s) is approved, it must be based on current exposures, not past exposures that are no longer experienced by U.S. residents, and must take into account the recognized fact that occupational exposures differ significantly based on the geographic location of mining deposits (*e.g.*, New York talc vs. talc from other U.S. or foreign deposits), and differ significantly for miners, millers, and processors.
1. The Board should request the documentation supporting the new talc nominations and review it to see whether the RoC procedures concerning support for nominations are being followed.

Regarding the potential revisions to the RoC review process discussed at the January meeting –

1. The Board should request and review the report and recommendations made to NTP by the external review panel (chaired by Prof. Lynn Goldman of Johns Hopkins).
1. The Board should recommend that the NTP advise the public as soon as possible of the status of the proposed revisions to the RoC review procedures.
1. The Board should recommend to the Director that revised review procedures require release of individual background documents to the public, and opportunity for public comments on such documents, prior to review of a nomination by RG1 and RG2.
1. The Board should recommend to the Director that revised procedures require providing the public with an opportunity to comment on proposed nominations before they are approved and the review process passes the point of no return.

We believe that the issues discussed above, and the recommendations for Board action, are very significant and merit careful attention by the full Board in view of their implications for the scientific integrity of the RoCs and compliance with the new Data Quality legislation and guidance.¹²

The talc review for the 10th RoC was very controversial and resulted in changes to the nominations made “on the fly” in the course of the RoC Subcommittee meeting, and we believe that if the actions outlined above are not taken, a new review based on the currently deficient

¹² We note that OMB’s proposed Data Quality guidance on peer reviews would apply to the RoC reviews, and that the proposed guidance would require that peer reviewers apply the Data Quality standards. Even if this is not stated explicitly in the final guidance, it seems obvious that it should be done.

nominations will be even more confusing and controversial and will almost certainly result in Data Quality challenges, both administratively and through the courts.

We hope that the Board will discuss these issues fully and candidly in public, and make appropriate recommendations to the NTP Director, at its June 29 meeting.

Respectfully,

/s/

William G. Kelly, Jr.
CRE Western Representative

Attachment

cc: Dr. Kenneth Olden, NTP Director

Attachment

Contact information: The primary contact for these comments is William G. Kelly, Jr. These comments are submitted on behalf of the Center for Regulatory Effectiveness. Mr. Kelly can be reached either through the contact information contained in the letterhead or at (208) 354-3050, wgkelly@tetontel.com.